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IgE-mediated hypersensitivity reactions are rare in patients with chronic helminth infections, even though FC_εRI-bearing cells are sensitized with anti-parasite IgE and are exposed – often continuously – to parasite antigens. This inhibition of allergic reactivity is mainly due to IgG4 blocking antibodies. IgG4 is unusually predominant among antifilarial antibodies (50–95% of the total IgG response). Depletion of IgG4 specifically removes the blocking activity from the sera of microfilaremic patients (1). A role of blocking IgG4 antibodies has also been suggested for successful allergen immunotherapy.

Blocking IgG4 competes with cell-bound IgE for allergen binding (2). Because IgG4 is functionally monovalent, does not fix complement, and binds weakly to Fc γ receptors, antigen binding by IgG4 has no or only minimally harmful consequences. However, competition between IgG4 and IgE can occur only if the two antibody isotypes have at least in part the same fine antigen specificity. A molecular mechanism for this overlap in specificity was indicated by the demonstration that isotype switching can occur sequentially from IgM to IgE via IgG4 (3). This finding

- 1) proved that two functionally antagonistic Ig isotypes, IgE and IgG4, can be induced by the same cytokine, IL-4
- 2) provided a rationale for the observation that IgE and IgG4 levels appear to be coregulated *in vivo*
- 3) implied that IL-4-dependent responses are not necessarily harmful and may be redirected so as to favour IgG4 over IgE.

Hence the commitment of our group to defining the molecular mechanisms of IgG4 and IgE coregulation. Our ultimate goal is to apply to allergy the lesson we learnt from helminth infections.

Our starting point was germline transcription, the crucial step for the determination of the isotype specificity of

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switching. The expression of germline transcripts reflects the cytokine-dependent activation of transcription from an I_H exon located upstream of the switch region subsequently targeted by recombination. Germline transcripts proceed from I_H through the switch region and the constant heavy chain (C_H) gene that will be expressed as a result of switching. After splicing, the I_H region is directly joined to the C_H transcript. Spliced germline transcripts *per se* and/or the mechanism of germline transcription are required to increase the accessibility of a specific switch region that becomes the preferred target for the recombination machinery [4].

Because the critical level for the determination of the isotype specificity of switching is germline transcription, any rational attempt at redirecting IL-4-dependent responses

away from IgE and toward IgG4 should be predicated on a full understanding of how the expression of ϵ and γ_4 germline transcripts is regulated, and what modifications IL-4 induces in the status of the chromatin of the IgG4 and IgE locus. We have dissected the ϵ germline promoter and characterized a number of transcription factors that contribute to its regulation [5, 6]. Furthermore we cloned the γ_4 germline transcripts and identified the γ_4 germline promoter [7]. In parallel, we are exploring the modifications in the accessibility of the γ_4 and ϵ loci induced by IL-4. We shall discuss similarities and differences between the ϵ and γ_4 promoters, as well as the identification of a functional link between germline transcription, isotype switching, and B-cell proliferation.

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